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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BLUMEL, BENJAMIN P	

ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/531,545	SIDDIQUI-JAIN, ADAM	
	Examiner	Art Unit	
	Benjamin P. Blumel	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6-12,15 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 6-12, 15 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/14/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants are informed that the rejections of the previous Office action not stated below have been withdrawn from consideration in view of the Applicant's arguments and/or amendments.

Claims 1, 2, 6-12, 15 and 16 are examined on the merits.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on February 14, 2007 was filed after the mailing date of the Non-final on January 26, 2007. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Upon applicants request, the examiner as also included an amended second page of the IDS submitted on August 8, 2005.

Claim Objections

Claim 6 is objected to because of the following informalities: the specific SEQ ID NO: for the claimed nucleotide sequence is missing. Appropriate correction is required.

Allowable Subject Matter

The indicated allowability of claims 5 and 6 are withdrawn in view of the newly discovered reference(s) to Genbank Accession #K02013 and Moore et al. (Nature Reviews: Molecular Cell Biology, 2000) and upon further consideration of the prior cited reference of Charneau et al. (US 6,682,907 B1). Rejections based on the newly cited reference(s) follow.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

(New Rejection) Claims 1, 2, 6, 8-10, 12, 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moore et al. (Nature Reviews: Molecular Cell Biology, 2000), Zennou et al. (Cell, 2000), Genbank Accession #K02013 and Charneau et al. (US 6,682,907 B1).

The instant invention is drawn to a method of identifying an antiviral candidate molecule that binds *in vitro* with a quadruplex structure within a central flap nucleic acid sequence of HIV-1 or HIV-2. The quadruplex structure is an intermolecular parallel structure formed by a dimmer of two intramolecular hairpin structures. The nucleic acid sequence comprises the nucleotide sequence of CAG_4AA (SEQ ID NO: 2) or $TTG_6TACAGTGCAG_4AA$ (SEQ ID NO: 3).

Moore et al. discuss various new targets for inhibiting HIV-1 replication. For example, Moore et al. teach inhibitors that target CD4-gp120/gp41 interactions or target nuclear importation through HIV DNA flap involvement. More specifically, Moore et al. teach the previously studied mutations of the HIV-1 DNA flap, which inhibited nuclear uptake of reverse transcribed HIV genome. Therefore, Moore et al. discuss how targeting the DNA flap with inhibitors could also provide a therapeutic treatment. However, Moore et al. do not teach the specifically claimed nucleotide sequences of the DNA flap, or the inherent features of such sequences (i.e. quadruplex-intermolecular parallel structure with a dimer of two hairpins. In addition, Moore et al. do not teach using cells from a subject, however, one skilled in the art would conduct such tests in a HIV receptive cell in order to determine the efficiency of the inhibitor with regard to DNA flap interruption.

As stated in the previous Office action, Zennou et al., which was referenced by Moore et al., studied the mutation of the DNA flap of HIV and its effects on nuclear importation of transcribed HIV genome (i.e. HIV DNA). As a result of mutating various nucleotides within the cPPT region of the DNA flap, Zennou et al. observed accumulation of unintegrated viral DNA in linear form, therefore reflecting the DNA flap's role in nuclear transport. Zennou et al. were also able to determine that a lack of a central DNA flap and its structural stability greatly inhibits import of the transcribed HIV genome.

As stated in the previous Office action, Charneau et al. disclose a HIV DNA sequence, which contains the claimed sequences of SEQ ID NO:s 2 and 3 of the instant invention at positions 36-42 and 21-42 of SEQ ID NO: 33, respectively. Charneau et al. also discusses the involvement of cPPT (containing the claimed SEQ ID NO:s 2 and 3) regions of HIV in nuclear import of the transcribed HIV genome, which Charneau et al. displays in figures 11F and 11G.

The Genbank accession #K02013 represents the complete genome of HIV-1 strain BRU. This isolate, like many other HIV strains contains within in the center of its genome, the DNA flap that contains the sequences of SEQ ID NO:s 2 and 3. With regard to this isolates, SEQ ID NO:s 2 and 3 are found at positions 4398-4405 and 4383-4405, respectively. In addition, Lyonnais et al. (Nucleic Acids Research, 2002) confirms that the HIV-1 central DNA flap of the Bru isolate includes the claim nucleic acid sequences of SEQ ID NO:s 2 and 3. Lyonnais et al. presents these sequence motifs in Table 1 with ODN2 and ODN3 containing these sequences. In addition, Lyonnais et al. also discusses the inherent ability of these sequences to form quadruplex, intermolecular hairpin dimers between the G-motifs of these DNA flap ODNs.

It would have been obvious to one of ordinary skill in the art to modify the methods taught by Moore et al. in order to identify an antiviral compound that binds to the central DNA flap of HIV, which contains the sequences of SEQ ID NO:s 2 or 3. One would have been motivated to do so, given the suggestion by Moore et al. that the method be used to identify substances that can inhibit the activity of the DNA flap. There would have been a reasonable expectation of success, given the knowledge that the central DNA flap of HIV is necessary for trafficking of its genome into the nucleus of a host cell in order for genomic integration to take place, as taught by Zennou et al., that the cPPT domain of HIV contains the sequences of SEQ ID NO:s 2 and 3 as taught by Charneau et al. and Genbank #K02013. In addition, based on the teachings of Lyonnais et al. as they pertain to the HIV isolate represented by Genbank Accession # K02013 and as the are applied to the sequence taught by Charneau et al., the claimed quadruplex, intermolecular hairpin dimers are an inherent feature of the central DNA flap which contains the claimed sequences of SEQ ID NO:s 2 and 3. Thus the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1, 2, 6, 8-12, 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hotoda et al. (Journal of Medicinal Chemistry, 1998) in view of Moore et al. *supra*, Zennou et al. *supra*, Genbank Accession #K02013 and Charneau et al. *supra*.

The claimed invention as discussed above, also involves the detection of binding of the candidate molecule with the central flap sequence by circular dichroism (CD) analysis.

The combined references above do not teach analyzing the binding of the candidate molecule to the central flap by CD.

Hotoda et al., as discussed in the pervious Office action, teach the screening for an anti-HIV-1 oligomer conjugate. Hotoda et al. tested multiple 15-mers complementary to different sites of HIV-1 RNA resulting in one active compound specific to the *tat* region of HIV-1. The findings of Hotoda et al. revealed that an aromatic group at the 5' end of the 15-mer greatly increased its anti-viral properties by interfering with the viral adsorption and cell fusion. Hotoda et al. utilized CD to analyze the candidate, a common method of analyzing proteins and nucleic acids.

Therefore, as discussed above, it would have been obvious to one of ordinary skill in the art to modify the method taught by Moore et al. in view of Zennou et al., Genbank Accession #K02013 and Charneau et al. in order to analyze candidate molecule-central DNA flap interactions by CD. One would have been motivated to do so, given the suggestion by Moore et al. that the method be used to identify substances that can inhibit the activity of the DNA flap. There would have been a reasonable expectation of success, given the knowledge that analyzing candidate antiviral substances, particularly proteins and nucleic acids can be accomplished with CD, as taught by Hotoda et al. Thus the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1, 2, 6-10, 12, 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sundquist et al. (PNAS, 1993) in view of Moore et al. *supra*, Zennou et al. *supra*, Genbank Accession #K02013 and Charneau et al. *supra*.

The claimed invention as discussed above, also involves incubating the nucleic acid in a solution comprising potassium ions.

The combined references above do not teach incubating the nucleic acid of SEQ ID NO:s 2 and 3 in potassium ions.

Sundquist et al. observed the stable formation of guanine hairpin dimer structures of an antiparallel helix within the genome of HIV. Sundquist discuss the importance of potassium ions stabilizing the intermolecular structures formed by the guanine dimers. In addition, Lyonnais et al. *supra,* confirms the teachings of Sundquist et al., that potassium ions stabilized the quadruplex structures formed from the central DNA flap of HIV isolate Bru.

Therefore, as discussed above, it would have been obvious to one of ordinary skill in the art to modify the method taught by Moore et al. in view of Zennou et al., Genbank Accession #K02013 and Charneau et al. in order to incubate the sequences of SEQ ID NO:s 2 or 3 with potassium ions. One would have been motivated to do so, given the suggestion by Moore et al. that the method be used to identify substances that can inhibit the activity of the DNA flap. There would have been a reasonable expectation of success, given the knowledge that the central potassium ions stabilize hairpin dimers of HIV, as taught by Sundquist et al. and confirmed by Lyonnais et al. Thus the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Summary

No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Benjamin P. Blumel whose telephone number is 571-272-4960. The examiner can normally be reached on M-F, 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-1600. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Benjamin P Blumel/
Examiner
Art Unit 1648

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